II. Rejection of Claims 1-3 and 6-10 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 and 6-10 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

As set forth in Applicants' response mailed on March 26, 2003 ("the previous response") to the First Office Action in this case, which was mailed on December 27, 2002 ("the First Action"), the present invention has a number of substantial and credible utilities, not the least of which is in diagnostic assays, as described in the specification, at least at page 11, line 9. As described in the specification at page 16, lines 10-24, the present sequence defines several coding single nucleotide polymorphisms - specifically, a C/G polymorphism at nucleotide position 1684 of SEQ ID NO:1, which can result in a leucine or phenylalanine being present at corresponding amino acid position 628 of SEQ ID NO:2; an A/G polymorphism at nucleotide position 2072 of SEQ ID NO:1, which can result in a serine or asparagine being present at corresponding amino acid position 691 of SEQ ID NO:2; an A/G polymorphism at nucleotide position 2120 of SEQ ID NO:1, which can result in an asparagine or serine being present at corresponding amino acid position 707 of SEQ ID NO:2; and an A/G polymorphism at nucleotide position 2540 of SEQ ID NO:1, which can result in a glycine or glutamate being present at corresponding amino acid position 847 of SEQ ID NO:2. As such polymorphisms, and particularly combinations of polymorphisms, are the basis for forensic analysis, which does not require any information at all about the ultimate biological function of the encoded protein, and is undoubtedly a "real world" utility, the present sequences must in themselves be useful.

The Examiner questions this asserted utility, stating "the presence of polymorphisms in human DNA is well established and virtually any locus on a human chromosome will exhibit one or more polymorphisms which could be so used" (Action at page 3). This argument is flawed in a **number** of respects. First, until a polymorphic marker is actually described it cannot be used in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence will contain a polymorphism and thus be useful in forensic analysis, until such a polymorphism is actually identified and described, such a likelihood is **meaningless**. The Examiner appears to be attempting to use the information presented for the first time by Applicants in the instant specification as hindsight verification that the presently claimed sequence would be expected to have polymorphic markers. Such hindsight

analysis based on Applicants discovery is completely improper. Second, the Examiner appears to be confusing the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an improper standard. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Importantly, the holding in the *Carl Zeiss* case is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument, which is presumably why the Examiner failed to address the holding of *Carl Zeiss* in the Action. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner further states that "Applicants have not identified any particular reason for use of this particular sequence in forensic analysis or any particular benefit that would derive

from analysis of a polymorphism in said sequence" (Action at page 3). Applicants respectfully point out that the presently described polymorphisms are useful in forensic analysis for the same reason that any marker is useful in forensic analysis - specifically, to specifically identify individual members of the human population based on the presence or absence of the described polymorphism. Using the polymorphic markers as described in the specification as originally field can distinguish members of a population from one another. In the worst case scenario, each of these markers are useful to distinguish 50% of the population (in other words, the marker being present in half of the population). The ability to eliminate 50% of the population from a forensic analysis **clearly** is a real world, practical utility. As set forth in *In re Langer* (183 USPQ 288 (CCPA 1974); "*Langer*"):

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, absent such evidence from the Examiner concerning the use of the presently described polymorphisms in forensic analysis, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, as the Examiner admits that the presently described polymorphism is a part of the family of polymorphisms that have a "well established" utility, the Federal Circuit's holding in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is directly on point. In *Brana*, the Federal Circuit admonished the Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. As set forth above, the present polymorphisms are useful in forensic analysis exactly as they are described in the specification as originally filed, without the need for any further research. Even if the use of these polymorphic markers provided additional information on the percentage of particular subpopulations that contain this polymorphic marker, this would not mean that "additional research" is needed in order for this marker as it is presently described in the instant specification to be of use to forensic science. As stated above, using the polymorphic marker as described in the specification as originally field can definitely distinguish members of a population from one another. However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well

settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as set forth in the previous response, the present sequence has a number of additional patentable utilities, among them, as detailed in the specification as originally filed, on page 2, lines 30-32, the present nucleotide sequences have a specific utility in "identification of coding sequence". This is evidenced by the fact that SEQ ID NO:1 can be used to map the 19 coding exons on chromosome 10 (present within three overlapping chromosome 10 clones; GenBank Accession Numbers AC024258, AL512429 and AC016395; alignments and the first page from each of the GenBank reports are presented in **Exhibit B**). It is well known that intron/exon boundaries are mutational hot spots, and thus the identification of the actual splice sites is of great utility to the skilled artisan. The specification details, at page 11, lines 9-14, that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics". Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed polynucleotides, as described in the specification at least at page 2, lines 32-33, the present nucleotide sequences have a specific utility in "mapping a unique gene to a particular chromosome". This is evidenced by the fact that SEQ ID NO:1 can be used to map the 19 coding exons on chromosome 10, as detailed above (**Exhibit B**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 10 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such

techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is invited to review, for example, section 3 of Venter *et al.* (2001, Science *291*:1304, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action also questions these asserted utilities, stating that "applicants have not identified any particular reason for identifying the coding sequence or using this polynucleotide in mapping chromosome 10" (Action at page 3). The Examiner once again seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 10 does not mean that the use of Applicants' sequence to map the protein coding regions of chromosome 10 is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

In the previous response, Applicants detailed an additional example of the utility of the present nucleotide sequences, as described in the specification from page 5, line 32 to page 6, line 2, specifically that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. As previously set forth, evidence of the "real world"

substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments from genes in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. Affymetrix is clearly a "real world" company, as evidenced the fact that the United States Patent and Trademark Office has issued numerous U.S. Patents to Affymetrix covering gene chip technology, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). Given the widespread utility of such "gene chip" methods using non-biologically validated, *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* biologically validated coding sequence would have great utility in such DNA chip applications. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Furthermore, compositions that enhance the utility of such DNA chips must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action also questions this utility, stating that "Applicants have also not identified any particular reason for use of this particular polynucleotide in "DNA chips" (Action at page 3). First, Applicants point out that nucleic acid sequences are commonly used in gene chip applications without **any** information regarding the function of the encoded protein, or even evidence regarding whether the sequence is actually even expressed. Thus, the present sequence, which has been biologically validated to be expressed, has a much greater utility than sequences that are merely predicted to be expressed based on bioinformatic analysis. Additionally, Applicants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. Expression profiling does **not** require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Furthermore, although further information regarding the biological activity of a particular nucleic

acid sequence might make it even more useful in gene chip applications, this does not mean that the use of the presently claimed nucleic acid sequence in gene chip applications is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Additionally, in the previous response, Applicants pointed out that a sequence sharing nearly 100% percent identity at the protein level over the entire length of the claimed sequence was present in the leading scientific repository for biological sequence data (GenBank), and had been annotated by third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens myopalladin" (GenBank accession number AF328296; alignment and GenBank report shown in **Exhibit C**). Additionally, Applicants pointed out that myopalladin had been shown by these scientists to be involved in muscle structure (Bang *et al.*, 2001, J. Cell Biol. *153*:413-427; **Exhibit D**). The Examiner states that "(b)ased on the alignment of the protein encoded by SEQ ID NO:1 with GenBank Acc# AF328296 and the report of Bang et al, (*sic*) 2001, the identity of said protein as myopalladin is credible", but that "this argument constitutes only hindsight reasoning" that "lacks any assertion of function" (Action bridging pages 3 and 4). Applicants respectfully disagree. In the specification as originally filed, Applicants described the described sequences as "structural proteins" (specification at page 1, line 10; see also page 1, lines 21-22), specifically "muscle proteins" (specification at page 2, line 3) and more specifically "titin-like protein" (specification at page 2, line 9, and page 16, line 11). Titin is a structural component of muscle that was well-known at the time the present application was filed, as evidenced by more than 100 publications in PubMed that included "titin" in the title published prior to the March 27, 2000 priority date of the present application. Thus, the function of the presently claimed sequence as a muscle structural protein was clearly asserted by Applicants in the specification as originally filed, which is all that is required to satisfy the requirements of 35 U.S.C. § 101. The citation of GenBank accession number AF328296 and the Bang *et al.* article merely **confirm** Applicants assertion of utility as set forth in the specification as originally filed. As set forth by Applicants in the previous response, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation and reference, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is a muscle structural protein. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, as set forth in the previous response, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-3 and 6-10 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1-3 and 6-10 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 and 6-10 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-3 and 6-10 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 1-3 and 6-10 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-3 and 6-10 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

The Examiner states that the specification "is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus" (Action bridging pages 5 and 6). The Examiner seems to be requiring a complete and exact description of every member of the claimed genus in order to comply with the requirements of 35 U.S.C. § 112, first paragraph. Applicants respectfully point out that this is **not** the standard for compliance with 35 U.S.C. § 112, first paragraph. As clearly set forth in the *Regents of Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), the Federal Circuit stated that:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can **distinguish** such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus (emphasis added).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to **distinguish** the genus

from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. Using the nucleic acid sequence of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides that encode at least 2000 contiguous nucleotides from SEQ ID NO:1 are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claim 1 thus meets the written description requirement.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, Applicants submit that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, has been overcome, and request that the rejection be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Swope have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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